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A NEW ROUTE FOR THE CONVENIENT SYNTHESIS OF 3-(THIAZOL-2'-YLTHIO)-2H-1-BENZOPYRAN-2-ONES

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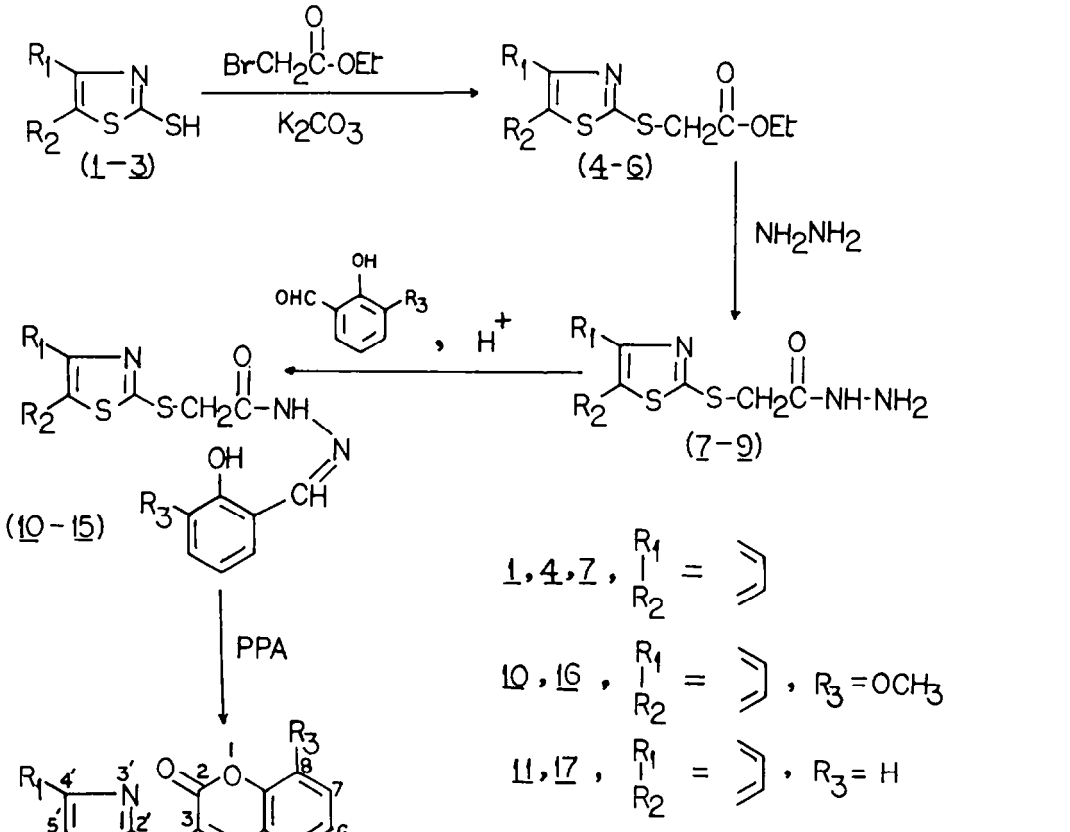
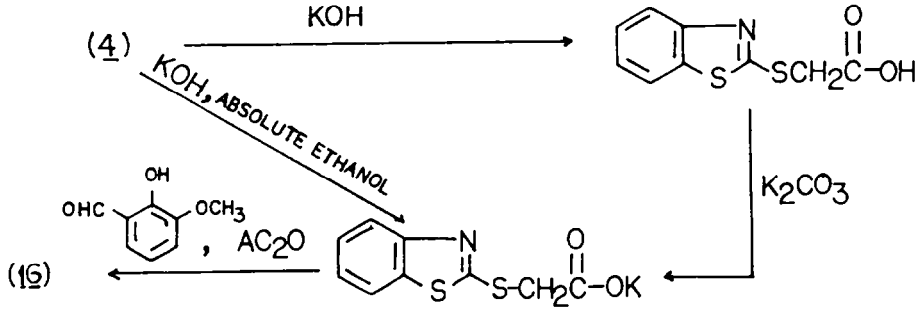
Abstract- Different thiazolylthiocoumarins were prepared by the reaction of (thiazol-2-ylthio) acetic acid hydrazides with 2-hydroxybenzaldehydes, followed by cyclization of the formed N-benzylidene derivatives in presence of PPA.

A variety of coumarins[1,2], thiazoles[3,4] and thiazolylcoumarins[5-9] derivatives have been reported for their importance in pharmaceutical, therapeutic and commercial fields. Although a number of methods have been reported for the synthesis of thiazolylcoumarins[5-9], the title compounds have not so far been synthesised.

In this paper we describe a new route for the synthesis of thiazolylthiocoumarins involving the cyclization of the N-benzylidene derivatives of (thiazol-2-ylthio)acetic acid hydrazides in presence of PPA. Treatment of appropriate 2-mercaptothiazoles (1, 2-3[10]) with ethyl bromoacetate gave the corresponding ethyl(thiazol-2-ylthio)acetates(4[11], 5, 6), which on reaction with hydrazine afforded the required (thiazol-2-ylthio)acetic acid hydrazides (7[12], 8, 9). Compounds (7-9) when treated with 2-hydroxybenzaldehydes in presence of few drops of acetic acid gave the corresponding N-benzylidene derivatives (10-15) in 92-96% yield. Structures of these compounds were assigned on the basis of spectral data and elemental analysis. In a typical case the N-benzylidene derivative of (benzothiazol-2-ylthio)acetic acid hydrazide (10) was heated with PPA to give a light yellow product (m.p. 172-173°C) in 75% yield. This compound was insoluble in cold dil. alkali, but dissolved on warming and recovered unchanged on acidification. This indicated the presence of a coumarin ring. This was further confirmed by its IR spectral data which showed the presence of a coumarin carbonyl (1725 cm^{-1}) and 3,4-double bond (1600 cm^{-1}). In the ^{1}H NMR spectrum of this compound, besides other signals, a singlet was observed at δ 8.20 for H-4 of the coumarin. On this basis this compound was assigned the structure 3-(benzothiazol-2'-ylthio)-8-methoxy-2H-1-benzopyran-2-one (16). This structure has also been proved by its ^{13}C NMR spectral data (see experimental). Finally the structure was confirmed by its comparison with an authentic sample, prepared by Perkin condensation of potassium (benzothiazol-2-ylthio)acetate (22) (obtained either by hydrolysis of 4 with potassium hydroxide to give the carboxylic acid, followed by conversion into potassium salt by treatment with potassium carbonate or direct from 4 by treating with potassium hydroxide in absolute ethanol) with 2-hydroxy-3-methoxybenzaldehyde

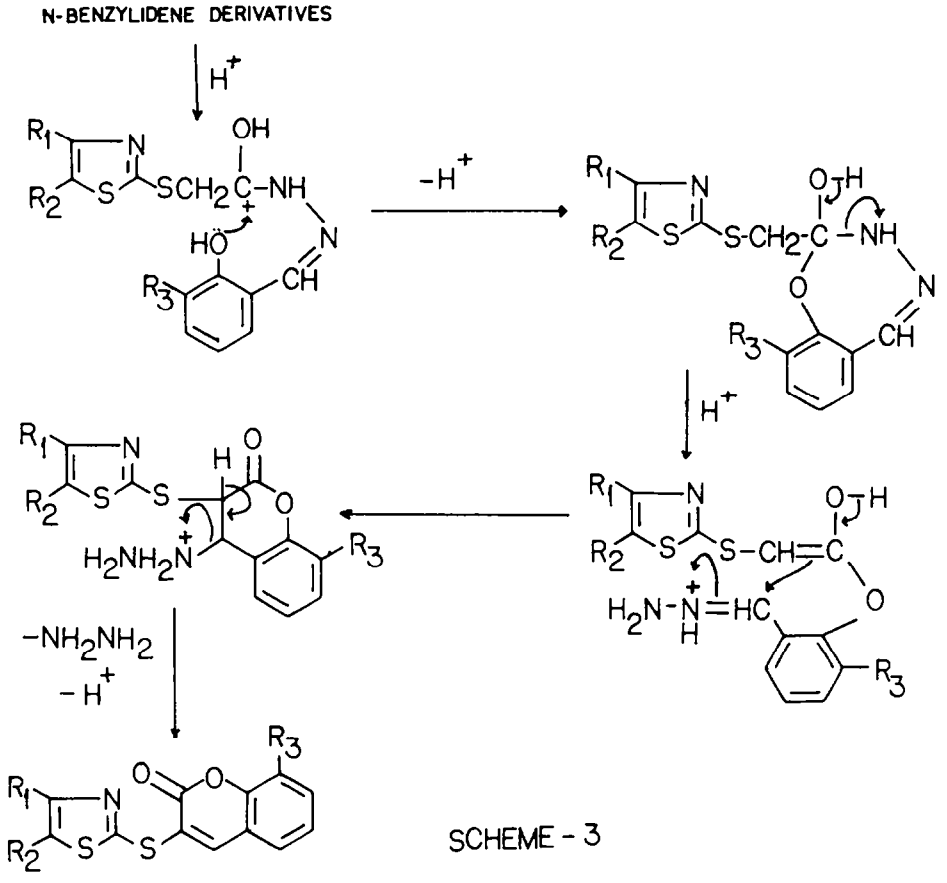


SCHEME-1



SCHEME-2

(Scheme-2). Compounds (17-21) were prepared in a similar way and structures were confirmed on the basis of spectral data and elemental analysis. Further these were compared with their authentic samples (co-TLC, co-IR, m.p., mix m.p.). A mechanism is proposed for the final cyclization step (Scheme-3). This is the first report for the synthesis of title compounds.



SCHEME - 3

EXPERIMENTAL

M.ps were taken in a sulphuric acid bath and are uncorrected ^{1}H NMR spectra were recorded on a Perkin-Elmer R-32 (90 MHz) instrument using TMS as the internal standard. IR and ^{13}C NMR spectra were recorded on Perkin Elmer Grating IR spectrophotometer model 627 and Jeol-JNM-FX 200 FT (50.10 MHz) respectively. Silica gel (60-120 mesh) was used for all chromatographic purifications.

Ethyl [4-(4'-methylphenyl)thiazol-2-ylthio]acetate (5)

Yield 96%; Light yellow solid; m.p. 42-43°C (benzenepetroleum ether); ^{1}H NMR ($CDCl_3$) δ 1.20 (3H,t,J = 7Hz $CH_2\underline{CH_3}$), 2.31 (3H, s, CH_3-4'), 3.99 (2H, s, CH_2), 4.20 (2H, q, J = 7Hz, $\underline{CH_2}CH_3$), 7.08 (2H, d, J = 9Hz, H-3' and 5'), 7.20 (1H,s,H-5), 7.65 (2H, d J = 9Hz H-2' and 6'); Found: C, 57.3; H, 4.9; N, 4.7. Calcd for $C_{14}H_{15}NO_2S_2$ C, 57.3; H, 5.1; N 4.7%.

Ethyl [4-(4'-methoxyphenyl)thiazol-2-ylthio]acetate (6)

Yield 97%; Yellow solid; m.p. 76-77°C (benzene-petroleum ether); ^{1}H NMR ($CDCl_3$) δ 1.30 (3H, t, J = 7Hz, $CH_2\underline{CH_3}$), 3.85 (3H, s, OCH_3-4'), 4.05 (2H, s, CH_2), 4.20 (2H, q, J = 7Hz, $\underline{CH_2}CH_3$), 6.94 (2H, d, J = 9Hz, H-3' and 5'), 7.20 (1H, s, H-5), 7.75 (2H, d, J= 9Hz, H-2' and 6'); Found: C, 54.2; H, 4.8; N, 4.6. Calcd for $C_{14}H_{15}NO_3S_2$: C, 54.3; H, 4.8; N, 4.5%.

[4-(4'-methylphenyl)thiazol-2-ylthio]acetic acid hydrazide (8)
Yield 87%; Colourless needles; m.p. 116-117°C (ethanol); ^{1}H NMR ($CDCl_3$) δ 2.38 (3H, s, CH_3-4'), 3.75 (2H, br s, exchanged with D_2O, NH_2), 3.90 (2H, s, CH_2), 7.17 (2H, d, J = 9Hz, H-3' and 5'), 7.25 (1H, s, H-5), 7.65 (2H, d, J = 9Hz, H-2' and 6'), 8.80 (1H, br s, exchanged with D_2O, NH); Found: C, 51.4; H, 4.6; N, 15.1. Calcd for $C_{12}H_{13}N_3OS_2$: C, 51.6; H, 4.6; N, 15.0%.

[4-(4'-methoxyphenyl)thiazol-2-ylthio]acetic acid hydrazide (9)
Yield 85%; Colourless needles; m.p. 145-146°C (ethanol); ^{1}H NMR ($CDCl_3$) δ 3.85 (3H, s, OCH_3-4'), 3.91 (2H, br s, exchanged with D_2O, NH_2), 3.96 (2H, s, CH_2), 6.95 (2H, d, J = 9Hz, H-3' and 5'), 7.25 (1H, s, H-5), 7.75 (2H, d, J = 9Hz, H-2' and 6'), 8.75 (1H, br s, exchanged with D_2O, NH); Found: C, 48.7; H, 4.4; N, 14.1. Calcd. for $C_{12}H_{13}N_3O_2S_2$: C, 48.8; H, 4.4; N, 14.2%.

N-(2"-Hydroxy-3"-methoxy)benzylidene derivative of 7(10)
General Procedure - 7(1.19 g, 5.0 mmol) was refluxed on steam bath with 2-hydroxy-3-methoxybenzaldehyde (0.76 g, 5.0 mmol) in presence of few drops of acetic acid in ethanol for 2h. The solid was separated out on cooling. It was filtered and recrystallised from ethanol to give 10 as colourless needles (1.78g). Yield 96%; m.p. 182-183°C; ^{1}H NMR ($CDCl_3$+TFA) δ 3.98 (3H, s, OCH_3-3"), 4.48 (2H, s, CH_2), 7.00-7.50 (3H, m, H-5, 6 and 4"), 7.70-8.15 (4H, m, H-4,7,5" and 6"), 8.70 (1H, s, =CH-); Found: C, 54.5; H, 4.0; N, 11.2. Calcd for $C_{17}H_{15}N_3O_3S_2$: C, 54.6; H, 4.0; N, 11.2%.

N-(2"-Hydroxy)benzylidene derivative of 7(11)
Yield 97%; White needles; m.p. 184-185°C (ethanol); ^{1}H NMR ($CDCl_3$+TFA) δ 4.50 (2H, s, CH_2), 7.10-8.20 (8H, m, H-Ar), 8.65 (1H, s, =CH-); Found: C,55.7; H,3.8; N, 12.2 . Calcd for $C_{16}H_{13}N_3O_2S_2$: C, 55.9; H, 3.7; N, 12.2%.

N-(2"-Hydroxy-3"-methoxy)benzylidene derivative of 8(12)
Yield 92%; light yellow needles; m.p. 171-172°C (ethanol); ^{1}H NMR ($CDCl_3$ + TFA) δ2.43 (3H, s, CH_3-4'), 3.95 (3H, s, OCH_3-3"), 4.32 (2H, s, CH_2), 7.10-7.80 (8H, m, H-Ar), 8.60 (1H, s, =CH-); Found: C, 58.0; H, 4.7; N, 10.1. Calcd for $C_{20}H_{19}N_3O_3S_2$: C, 58.1; H, 4.6; N, 10.1%.

N-(2"-Hydroxy)benzylidene derivative of 8(13)
Yield 96%; Colourless needles; m.p. 184-185°C (ethanol); ^{1}H NMR ($CDCl_3$ + TFA) δ 2.45 (3H, s, CH_3-4'), 4.35 (2H, s, CH_2), 7.00-7.90 (9H, m, H-Ar), 8.51 (1H, s, =CH-); Found: C, 59.6; H, 4.4; N, 10.9. Calcd for $C_{19}H_{17}N_3O_2S_2$: C, 59.5; H, 4.4; N, 10.9%.

N-(2"-Hydroxy-3"-methoxy)benzylidene derivative of 9(14)
Yield 95.5%; light yellow needles; m.p. 180-181°C (ethanol); ^{1}H NMR ($CDCl_3$+TFA) δ3.90 (3H, s, OCH_3-4'), 3.96 (3H, s, OCH_3-3"), 4.32 (2H, s, CH_2), 7.00-7.30 (5H, m, H-3',5',4",6" and 5), 7.50-7.75 (3H, m, H-2', 6' and 5"), 8.60 (1H, s, =CH-); Found: C, 55.7; H, 4.6; N, 9.5. Calcd for $C_{20}H_{19}N_3O_4S_2$: C, 55.9; H, 4.4; N, 9.7%.

N-(2"-Hydroxy)benzylidene derivative of 9(15)
Yield 96%; light yellow needles; m.p. 172-173°C (ethanol); ^{1}H NMR ($CDCl_3$ + TFA) δ3.99 (3H, s, OCH_3-4'), 4.35 (2H, s, CH_2), 7.00-7.90 (9H, m, H-Ar), 8.52 (1H, s, =CH-); Found C, 57.3; H, 4.2; N, 10.5. Calcd for $C_{19}H_{17}N_3O_3S_2$: C, 57.1; H, 4.2; N, 10.5%.

3-(Benzothiazol-2'-ylthio)-8-methoxy-2H-1-benzopyran-2-One (16)
Method I, General Procedure
10 (1.86 g, 5.0 mmol) was heated with polyphosphoric acid (5.0 ml) at 100°C for 15h. The reaction mixture was then treated with crushed ice and the solid

thus obtained purified by column chromatography (2:3 benzene-petroleum ether) to give 16 as yellow needles (1.27 g) yield 75%; m.p. 172-173°C; ^{1}H NMR ($CDCl_3$) δ3.97 (3H, s, OCH_3-8), 7.00-8.05 (7H, m, H-Ar), 8.20 (1H, s, H-4); ^{13}C NMR ($CDCl_3$) 56.0 (q, OCH_3-8), 114.2, 119.3, 121.0, 122.5, 125.0, 125.5 and 126.0 (each d, C-Ar), 119.3, 135.0, 143.0, 147.0, 147.2, 153.0 and 158.2 (each s, C-Ar), 146.0 (d, CH-4), 162.0 (s, C=O); ν_{max}^{KBr} 1725 cm^{-1} (C=O); Found: C, 59.9; H, 3.2; N, 3.9. Calcd for $C_{17}H_{11}NO_3S_2$: C, 59.8; H, 3.2; N, 4.2%.

3-(Benzothiazol-2'-ylthio)-2H-1-benzopyran-2-one (17)

Yield 92%, yellow needles; m.p. 170-171°C; ^{1}H NMR[$(CD_3)_2S$=O] δ 7.15-7.95 (8H, m, H-Ar), 8.65 (1H, s, H-4); ν_{max}^{KBr} 1720 cm^{-1} (C=O); Found: C, 61.8; H, 2.9; N, 4.6. Calcd for $C_{16}H_9NO_2S_2$: C, 61.7; H, 2.8; N, 4.5%.

3-[4'-(4"-Methylphenyl)thiazol-2'-ylthio]-8-methoxy-2H-1-benzopyran-2-one (18)

Yield 50%; yellow needles; m.p. 135-136°C; ^{1}H NMR ($CDCl_3$) δ 2.35 (3H, s, CH_3-4"), 3.90 (3H, s, OCH_3-8), 6.90-7.75 (8H, m, H-Ar), 7.80 (1H, s, H-4); ν_{max}^{KBr} 1715 cm^{-1} (C=O); Found: C, 62.8; H,3.9; N, 3.7. Calcd for $C_{20}H_{15}NO_3S_2$: C, 62.9; H, 3.9; N, 3.6%.

3-[4'-(4"-Methylphenyl)thiazol-2'-ylthio]-2H-1-benzopyran-2-one (19)

Yield 60%; yellow needles; m.p. 175-176°C; ^{1}H NMR ($CDCl_3$) δ 2.45 (3H, s, CH_3-4"), 7.12 (2H, d, J = 9Hz, H-3" and 5"), 7.30-7.80 (5H, m, H-Ar), 7.80 (2H, d, J=9Hz, H-2" and 6"), 7.95 (1H, s, H-4); ν_{max}^{KBr} 1700 cm^{-1} (C=O); Found: C, 64.8; H, 3.8; N, 3.7. Calcd for $C_{19}H_{13}NO_2S_2$: C, 64.9; H, 3.7; N, 3.9%.

3-[4'-(4"-Methoxyphenyl)thiazol-2'-ylthio]-8-methoxy-2H-1-benzopyran-2-one (20)

Yield 37%; light yellow needles; m.p. 175-176°C; ^{1}H NMR ($CDCl_3$) δ 3.90 (3H, s, OCH_3-4"), 4.00(3H, s, OCH_3-8), 6.90-7.80 (8H, m, H-Ar), 7.90 (1H, s, H-4); ν_{max}^{KBr} 1710 cm^{-1} (C=O); Found: C,60.5; H, 3.5; N, 3.5. Calcd for $C_{20}H_{15}NO_4S_2$: C, 60.4; H, 3.7; N, 3.5%.

3-[4'-(4"-Methoxyphenyl)thiazol-2'-ylthio]-2H-1-benzopyran-2-one (21)

Yield 40%, yellow needles; m.p. 163-164°C; ^{1}H NMR ($CDCl_3$) δ 3.90 (3H, OCH_3-4"), 7.00 (2H, d, J = 9Hz, H-3" and 5"), 7.25-7.65 (5H, m, H-Ar), 7.90 (2H, d, J=9Hz, H-2" and 6"), 7.96 (1H, s, H-4); ν_{max}^{KBr} 1710 cm^{-1} (C=O); Found: C, 62.2; H, 3.6; N, 3.8. Calcd for $C_{19}H_{13}NO_3S_2$: C, 62.1; H, 3.5; N, 3.8%.

3-(Benzothiazol-2'-ylthio)-8-methoxy-2H-1-benzopyran-2-one (16)

Method II, General procedure -

Potassium (benzothiazol-2-ylthio)acetate (22) (1.31 g, 5.0 mmol), acetic anhydride (3 ml), 2-hydroxy-3-methoxybenzaldehyde (0.76 g, 5.0 m mol) was heated at 160-165°C for 4h. Reaction mixture was then treated with crushed ice and left overnight. The solid thus separated, was filtered and purified by column chromatography (2:5 benzene-petroleum ether) to give 16 as yellow needles (1.00 g) yield 58%; m.p. 172-173°C.

Compounds (17-21) were also prepared and found similar in all respects (^{1}H NMR, m.p., mix m.p., co-IR, T.L.C.).

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